REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

About two billion people are thought to be infected with the bacillus *Mycobacterium tuberculosis* ("Mtb"), the causative agent of tuberculosis ("TB"). The majority of those infected do not show signs of disease; however, each year about 8 million individuals develop active tuberculosis and about 2 million die. Cure of tuberculosis requires months of treatment with multiple anti-infective agents. Incomplete treatment is common and encourages the emergence of multi-drug resistant ("MDR") strains. MDR isolates are detected in all nations and prevalent in some. Infection can be acquired by sharing airspace with an individual with cavitary disease, with an infectious dose estimated at 1-10 inhaled bacilli.

Furthermore, Mtb is a bioterrorism threat, because it has high potential for generating public fear and economic disruption. Bioterrorists could send individuals with cavitary MDR-TB through mass transit networks. Although few of the people exposed would ever develop TB, and almost none would be sickened acutely, knowledge would spread that many of those exposed would be likely to become infected, and that if MDR-TB did develop, it would be difficult to treat and lethal in up to 35% of cases among otherwise healthy individuals, even given optimal care. This would discourage congregation in subways, buses, train stations, and airports, causing economic disruption. Even a handful of cases of MDR-TB could overwhelm a regional hospital system's capacity to provide isolation. The disease rate is low, but the infection rate is high when organisms are aerosolized in shared space. Aerosolization requires no technology, only coughing.

Mtb infection can persist for decades. The normal immune system creates an environment in which Mtb is not completely sterilized, yet replicates so little that 90% of immune-competent hosts who are infected with Mtb never develop overt TB. During latent infection, the primary residence of Mtb is the macrophage. The antimicrobial arsenal of the activated macrophage includes inducible NO synthase ("iNOS" or "NOS2"). At the acidic pH (< 5.5) prevalent in the phagosome of activated macrophages, nitrite, a major oxidation product of NO, is partially protonated to nitrous acid, which dismutates to form NO and another radical, NO_2. Thus, mildly acidified nitrite is a physiologic antimicrobial system. Reactive nitrogen intermediates ("RNI") may inflict not only nitrosative but also oxidative

injury, as when NO combines with superoxide from bacterial metabolism to generate peroxynitrite within the bacterium. Reagent NO kills Mtb with a molar potency exceeding that of most anti-tuberculosis drugs. In humans and mice with tuberculosis, macrophages in infected tissues and airways express enzymatically active iNOS. Mice lacking iNOS cannot control Mtb infection. Despite the protective effects of RNI, a small number of viable mycobacteria usually persist for the lifetime of the infected host, and sometimes resume growth.

Persistence of Mtb in those lacking overt disease is evidenced by the emergence of TB in patients with arthritis or Crohn's disease immunosuppressed by biologicals that neutralize TNF. More significantly, emergence of overt TB in people with subclinical Mtb infection reaches 50-80% with supervening HIV disease. Worldwide, TB may be the leading cause of death in AIDS patients, and TB exacerbates growth of HIV. Lifelong persistence of infection in immunocompetent hosts and exacerbation of infection in immunodeficient hosts suggest a dynamic balance. Inhibition of Mtb resistance pathways might tilt the balance in favor of the host, allowing the host to sterilize the pathogen and perhaps allowing conventional chemotherapy to kill the pathogen faster. Inhibition of the pathways by which Mtb resists the host might allow people who are subclinically infected to rid themselves of persistent bacilli, reduce their lifelong risk of reactivation TB, and interrupt the pandemic.

Among the most successful forms of anti-Mtb chemotherapy is that applied naturally by the host. Of these, nitric oxide ("NO") is the only molecule known to be produced by mammalian cells that can kill tubercle bacilli *in vitro* with a potency (~150 nM) comparable to that of chemotherapy. That the primary product of iNOS is mycobacteriacidal provides one type of evidence consistent with a role for iNOS in controlling tuberculosis. There are 4 more lines of evidence: (ii) immunologically activated, iNOS-expressing mouse macrophages can kill *M. tuberculosis*, but not if the macrophages are treated with iNOS inhibitors or bear disrupted NOS2 alleles; (iii) iNOS is expressed in infected mouse tissues in which the growth of Mtb is restrained, but iNOS is scant when immunosuppressive drugs or genetic interventions impair host resistance; (iv) healthy mice that harbor tubercle bacilli succumb abruptly to TB following ingestion of specific iNOS inhibitors; and (v) mice with disrupted NOS2 alleles die with fulminant TB in a few weeks, while wild type mice survive infection for ~9 months. When O_2 is limiting, Mtb uses nitrate as an electron acceptor, generating nitrite as a byproduct. This reaction is essential for mycobacterial proliferation in mouse lung, as judged by the failure of nitrate reductase-deficient BCG to proliferate even in

immunodeficient mice. Nitrate arises from dietary sources and the action of constitutively expressed NOS, and is thus a normal component of human blood and bronchoalveolar fluid. Nitrite regenerates NO at the mildly acidic pH pertaining in poorly oxygenated microenvironments. Thus, Mtb needs to survive nitrosative stress generated by itself as well as by the host.

The existing armamentarium against Mtb is clinically effective when the organism is drug-sensitive and 180-270 days of drug administration are ensured by directly observed therapy. Both conditions are hard to meet. Agents are urgently needed that target additional pathways. Most approaches to antibiotic development are based on screening for compounds that inhibit the growth of the organism in pure culture, or testing inhibitors of pathways already known to be essential for growth in pure culture. Rarely has an effort been made to screen under conditions that model a critical aspect of the host-pathogen relationship. For Mtb, intraphagosomal conditions include low $Fe2^{+}$, low $Mg2^{+}$, and increased oxidative/nitrosative stress. The clinical immunobiology of Mtb infection teaches that chemotherapy that is effective *in vitro* is less effective in the host whose immune system does not contribute to control. In the mouse, chemotherapy that works *in vitro* is only transiently effective in a host that lacks iNOS.

Thus, TB is the leading cause of death from a single bacterial infection and the leading opportunistic infection in HIV-infected hosts. Multiple drug resistance is rapidly spreading and exacerbates these burdens, and the threat of bioterrorism adds a new dimension to the picture. New chemotherapeutic options are needed that work faster and on additional targets than those now available. In particular, it would be useful to have more information about the genes that allow Mtb to resist host antibacterial mechanisms for the development of anti-infectives in the treatment of Mtb infection.

The present invention is directed to overcoming these and other deficiencies in the art.

It is the position of the U.S. Patent and Trademark Office ("USPTO") that the Information Disclosure Statement mailed Oct. 29, 2004, fails to comply with 37 CFR 1.98(a)(2) for having the citation for two references on line 9 on the accompanying form PTO/SB/08A. Applicants disagree.

The citation that appears on line 9 of the PTO/SB/08A mailed October 19, 2004, is Cole et al., "Deciphering the Biology of *Mycobacterium tuberculosis* from the Complete Genome Sequence," *Nature* 393:537-544 (1998)("Cole I"), *erratum Nature* 396:190-198 (1998) ("Cole II"). As a result of an error during film output, Cole I, as

published, contained errors in Table 1, Figure 2, and Figure 5b. Because Cole I is lacking portions of its intended disclosure, it is an incomplete reference standing alone. Cole II provides an description of the errors that occurred in Cole I, and provides a corrected version of Table 1, Figure 2, and Figure 5b from Cole I. See the attached copies of Cole I and Cole II at Exhibit 1. Thus, only by combining the disclosures of Cole I and Cole II does one obtain a complete and relevant disclosure. Therefore, the objection to Cole I and Cole II for being listed together on one line of the PTO/SB/08A as filed is improper. However, to reduce issues, Cole I and Cole II are separately listed on the attached PTO/SB/08A form. It is respectfully requested that these references be considered and the accompanying PTO/SB/08A from be initialed to reflect such consideration.

The objections to the title, the abstract, and the specification of the present application are respectfully traversed.

It is submitted that the title and abstract, as filed, are descriptive of the present invention. Since the claims are not limited to the features which the outstanding office action suggests adding, neither should the title or abstract be so limited. Indeed, for this very reason, such amendments would be misdescriptive.

Applicants submit that the above amendments to the specification, which replace the term "nucleotidase" with the term "nucleotide," are required to correct a typographical error in the specification, in which "nucleotidase" was inadvertently substituted for "nucleotide" in the phrase "nucleotide excision repair." Support for this amendment is found in the recitation of "*nucleotide* excision repair" in the specification at, *inter alia,* page 22, lines 19-21.

It is the position of the USPTO that the term "MLN-273" used in the specification for the protease inhibitor compound N-[4-morpholine]carbonyl-beta-1[1-naphthyl]-L-alanine-L-leucine boronic acid is confusing. Applicants disagree. Since the chemical name of the compound "MLN-273" is provided in the specification at paragraph [0039], one skilled in the art would have fully understood what was meant by the term "MLN-273."

The rejection of claims 1-6, 12-20, 63-68, and 74-87 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1, 12-20, 63, and 74-87 under 35 U.S.C. § 112 (2nd para.) for indefiniteness for the recitation of the term "proteasomal activity" is respectfully traversed.

Applicants submit that one of ordinary skill in the art, having read the present application, would have fully understood what is meant by "proteasomal activity" in claim 1. The present application describes with specificity what is meant by "proteasomal activity." For example, at pg. 12, lines 16-19, the specification discloses that "the proteosomal activity being inhibited is an AAA ATPase activity or a proteasomal protease activity." The present application teaches that AAA ATPases for inhibition include an AAA ATPase forming ring-shaped complex ("ARC"), a proteasome associated nucleotidase, a mycobacterial proteasome ATPase, and a proteasome accessory factor (pg. 12, lines 25-29), where the ARC may be a products of the Rv2115c Mtb, Rv2097c and the GroEL1 genes (pg. 12, lines 30-32). The present application further teaches that "proteasomal protease activity" includes the protease activity in a proteasome core including the prcBA genes, PrcA, and PrcB (pg. 12, lines 19-21). Thus, one of ordinary skill in the art, having read the present application, would have understood what was meant by "proteasomal activity" as recited in the claimed invention.

Therefore, the indefiniteness rejection of claims 1, 12-20, 63, and 74-87 under 35 U.S.C. § 112 (2nd para.) based on the term "proteasomal activity" is improper and should be withdrawn.

The rejection of claims 2-3 and 64-65 under U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of the term "proteasomal protease activity" in claims 2-3 and "protease activity" in claims 64-65 is respectfully traversed in view of the above amendments. As reflected in these claims, the proteasomal activity being inhibited can be AAA ATPase activity or proteasomal protease activity. Since one form of the claimed proteasomal activity is the claimed proteasomal protease activity and it is clear what that term means, the rejection of claims 2-3 and 64-65 under U.S.C. § 112 (2nd para.) for indefiniteness is improper and should be withdrawn.

The rejection of claims 3 and 65 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of the term "proteasome core" is respectfully traversed.

At the time the present invention was made, the terms "20S proteasome" and "proteasome core" were used interchangeably in the art. This arose from the nomenclature associated with the eukaryotic proteasome. For example, a review of eubacterial proteasomes discloses that: "[t]he 26S proteasome is a large ATP-dependent proteolytic complex found in the cytosol and nucleus of all eukaryotic cells" where "[t]he 26S complex consists of two asymmetric 19S caps flanking a barrel-shaped 20S core (*the 20S proteasome*) (Lupas et al., "Eubacterial Proteasomes," *Molecular Biology Reports* 24:125-131 (1997) at pg. 125, left

col., 1st two full para.) ("Lupas") (attached hereto as Exhibit 2) (emphasis added). This is supported by Nagy et al., "Further Sequence Analysis of the DNA Regions with the *Rhodococcus* 20S Proteasome Structural Genes Reveals Extensive Homology with *Mycobacterium leprae," DNA Sequence – The Journal of Sequencing and Mapping* 7:225-228 ("Nagy I") (attached hereto as Exhibit 3), which teaches that the "20S proteasome constitutes the proteolytic core" of the eukaryotic 26S proteasome (at 225, rt. col., lines 1-9). Further, Baumeister et al., "The Proteasome: Paradigm of a Self-Compartmentalizing Protease," *Cell* 92:367-380 (1998) ("Baumeister") (attached hereto as Exhibit 4) teaches that the 20S proteasomal core structure is conserved from archeabacteria to eukaryotes (pg. 368, 1st full para.); and Löwe et al., "Crystal Structure of the 20S Proteasome from the Archeon *T. acidophilum* at 3.4 Å Resolution," *Science* 286:533-539 (1995) ("Löwe") (attached hereto as Exhibit 5) teaches that the 20S proteasome forms the catalytic core of the 26S complex (pg. 533, left col.) In addition, the presence of 20S proteasomes in eubacteria, built of α and β subunits encoded by known nucleic acid sequences, have been identified in several species of actinomycetes (*see e.g.,* Wolf et al., "Characterization of ARC, a Divergent Member of the AAA ATPase Family from *Rhodococcus erythropolis*," *J Mol Biol* 277:13-25 (1998) at 14, left col., 1st full para.) (attached hereto as Exhibit 6) ("Wolf") and Nagy et al., "The 20S Proteasome of *Streptomyces Coelicolor*," *J Bacteriol* 180(20):5448-5453 (1998) at Abstract ("Nagy II") (attached hereto as Exhibit 7).

Thus, a skilled scientist, having read the present application, would understand what the term "proteasome core" meant and would have had a clear understanding of the structure of eubacterial 20S proteasomal core.

The rejection of claims 4-6 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of "wherein the protease . . ." is respectfully traversed in view of the above amendment to the claims.

The rejection of claims 4-6 and 64-68 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

Applicants submit that one of ordinary skill in the art would have understood that the present invention encompasses pathogens in addition to Mtb, because at the time the present invention was made, prcBA genes were known to be present in pathogens other than Mtb.

In particular, the actinomycetes *Rhodococcus erythropolis* was known to have prcBA genes, which encode the subunits of the 20S proteasome (Wolf at 14, left col., 1st full

para.). Furthermore, Nagy II teaches that *Streptomyces coelicolor* contained a 20S proteasome built from one α-type subunit (PrcA) and one β-type subunit (PrcB), characterized the structural genes of the *S. coelicolor* proteasome as having an operon-like gene organization, i.e, *prcBA,* similar to *Rhodococcus* and *Mycobacterium* spp. (*see* Abstract), and describes the enzymatic function associated with the prcBA genes in eubacteria (pg. 5450, para. beginning at bottom of left col., carrying over to rt. col., and Figure 4). Thus, one of skill in the art would have understood that prcBA genes are found in eubacteria in addition to Mtb; and that they encode proteolytic subunit of the 20S proteasome.

Therefore, the rejection of claims 4-6 and 64-68 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is improper and should be withdrawn.

The rejection of claims 12-14 and 82-84 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of the terms "oxidative/nitrosative stress" in claims 12 and 82, "reactive nitrogen intermediate-induced stress" in claims 13 and 83, and the term "reactive oxygen intermediate-induced stress" in claims 14 and 84 is respectfully traversed.

Firstly, applicants submit that the meaning of the terms "oxidative/nitrosative stress," "reactive nitrogen intermediate-induced stress," and "reactive oxygen intermediate-induced stress" were set forth and described in the present application. In particular, the specification describes the antimicrobial arsenal of pathogen-infected macrophages which results in nitrosative and oxidative injury to the pathogen through the production of reactive nitrogen intermediates (RNI) by the host cell, and the importance of this process in controlling Mtb infection in a subject (pg. 2, line 19 to pg. 3, line 15; pg. 4, lines 16-21).

Furthermore, the terms "oxidative/nitrosative stress," "reactive nitrogen intermediate-induced stress," and "reactive oxygen intermediate-induced stress" are well-known in the art. This is demonstrated by Nathan et al., "Reactive Oxygen and Nitrogen Intermediates in the Relationship Between Mammalian Hosts and Microbial Pathogens," *Proc Natl Acad Sciences USA* 97(16):8841-8848 (2000) ("Nathan") (attached hereto as Exhibit 8) and Lu et al., "The Global Regulator ArcA Controls Resistance to Reactive Nitrogen and Oxygen intermediates in *Salmonella enterica* Serovar Enteritidis," *Infection and Immunity* 70(2):451-461 (February, 2002) ("Lu") (attached hereto as Exhibit 9). Nathan defines the terms reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) (pg. 8841, 1st para., left col); teaches that ROI and RNI are highly toxic, chemically reactive micromolecules, produced by phagocytes and macrophages of mammals infected by

a microbial pathogen, which are aimed at preventing microbial metastasis (pg. 8841, right col, 1st and 2nd full para.); and provides a detailed list of known ROI and RNI chemical moieties (pg. 8841, 1st para., left col). Lu teaches that ROI and RNI products are essential to an effective immune defense response against microbes, and that the ability of the microbe to produce an appropriate response to these oxidative and nitrosative "stresses" in the environment determines the clinical outcome for an infected mammalian host (pg. 451, right col., first full para., to top of pg. 452; *see also* Abstract, last two sentences). Thus, one of ordinary skill in the art, having read the present application would have fully understood what was meant by "oxidative/nitrosative stress," "reactive nitrogen intermediate-induced stress," and "reactive oxygen intermediate-induced stress" as used in the claimed invention.

Accordingly, the rejection of claims 12-14 and 82-84 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is improper and should be withdrawn.

The rejection of claims 77 and 81 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of "DNA repair enzyme" (claim 77) and "flavin-like co-factor synthesis enzyme" (claims 77 and 81) is respectfully traversed.

With regard to the indefiniteness rejection of claim 77, applicants submit that one of ordinary skill in the art would have fully understood the meaning of "the term DNA repair enzyme."

DNA damage repair mechanisms and the enzymes related to DNA repair were well known at the time the present invention was made. Sancar, A., "DNA Excision Repair," *Annu Rev Biochem* 65:43-81 (1996) ("Sancar") (attached hereto as Exhibit 10), describes generally the three molecular mechanisms for repairing damaged DNA (direct repair, base excision repair, and nucleotide excision repair (NER)) and the enzymes that are involved in each mechanism (at pg. 44-47), then provides a detailed analysis of the NER mechanism (pg. 46-75). "Nucleotide Excision Repair in Prokaryotes," Chap. 5, pp. 191-232, *DNA Repair and Mutagenesis*, eds. Friedberg et al., ASM Press, Washington, DC (1995)("Friedberg") (attached hereto as Exhibit 11) discloses in extensive detail the structure and function(s) of enzymes involved in nucleotide excision repair of damaged DNA in prokaryotes, including the UvrABC damage-specific endonuclease of *E. coli* (pg. 192-209), UrvD (DNA helicase II) and Pol I (pg. 210-231), and others.

With regard to the indefiniteness rejection of claims 77 and 81, applicants submit that the above amendments to claim 77 and claim 81 are supported by pg. 23, lines 18-24 of the specification. Furthermore, one of ordinary skill in the art would have

understood what is meant by "a co-enzyme F420 biosynthesis enzyme," as recited in amended claims 77 and 81.

At the time the present invention was made, F420 coenzymes had been identified in Archea; aerobic Actinomycetes, including all species of *Mycobacterium*; and cyanobacteria (Bair et al., "Structures of Coenzyme F_{420} in *Mycobacterium* Species," *Arch Microbiol* 176:37-43 (2001) at pg. 37, left col., 1st full para. over to top of rt. col., and Table 2 at pg. 42 ("Bair") (attached hereto as Exhibit 12); Choi et al., "Demonstration That *fbiC* is Required by *Mycobacterium bovis* BCG for Coenzyme F(420) and FO Biosynthesis," *J Bacteriol* 184(9):2420-2428 (May 2002) at pg. 2420, left col., 1st full para. ("Choi") (attached hereto as Exhibit 13)). Furthermore, the structure and function of co-enzyme F420 had been elucidated (Bair at Abstract and pg. 37, 1st full para. of rt. col. to end of pg. 38, and Figures 1A-C; Choi at 2420, left col., 1st para., and Figure 1A; Isabelle et al., "Large-Scale Production of Coenzyme F420-5,6 by Using *Mycobacterium smegmatis*," Applied & Environmental Microbiology 68(11):5750-5755 (2002) at pg. 5750, left col., 1st full para. ("Isabelle") (attached hereto as Exhibit 14); the pathway of F420 biosynthesis mapped and the bacterial genes critical for F420 biosynthesis identified (White, RH., "Biosynthesis of Methanogenic Cofactors," *Vitamins and Hormones* 61:299-337 Academic Press (2001) at 324-328, 330, and Figures 9-10; ("White") (attached hereto as Exhibit 15); Choi at 2420, rt. col., 1st full para. and Figure 1 at 2421; *see also* 2422, rt. col. to top of 2433, left col.); and an assay for the determination of enzymes of the F420 synthesis pathway suggested (Bair at pg. 42, left col., last sentence). Thus, a skilled scientist, having read the present application, would have understood fully what was meant by "a co-enzyme F420 biosynthesis enzyme" in claims 71 and 88.

Accordingly, the rejection of claims 77 and 81 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is improper and should be withdrawn.

The rejection of claim 78 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

Firstly, claim 78, as amended, is drawn to a method "wherein the enzyme inhibited is a DNA repair enzyme in the form of a *nucleotide* excision-repair enzyme." Applicants submit that this amendment was required to correct a typographical error, wherein *nucleotidase* was inadvertently substituted for *nucleotide* in the specification and in claims 78-80.

Furthermore, applicants submit that one skilled in the art would have understood what was meant by a nucleotide excision repair ("NER") enzyme. Firstly, the specification teaches:

> [t]he two [*Mycobacterium tuberculosis*] mutants most susceptible to acidified nitrite contained transposon insertions in the nucleotide excision-repair (NER) gene uvrB. The NER system, consisting of UvrA, B, C and D, has been extensively studied in *E. coli* and is required for replacing nucleotides in DNA damaged by agents such as UV light.

(Pg. 22, lines 20-24). In addition, NER as a DNA repair mechanism was well-known in the art at the time the present invention was made, with the enzymes involved in NER being well characterized. For example, Theis et al., "The Nucleotide Excision Repair Protein UvrB, a Helicase-Like Enzyme with a Catch," *Mutation Research* 460:277-300 (2000) ("Theis") (attached hereto as Exhibit 16) teaches that NER is a universal DNA repair mechanism found in all three kingdoms of life (*see* Abstract) in which damaged DNA is repaired through excision of an oligonucleotide that contains the lesion (pg. 278, left col., 1st full para.). Theis provides a detailed disclosure of structure, function, and substrates of bacterial NER enzymes UvrA, UvrB, and UvrC (*see generally* pp. 278-298). Sancar (as discussed above) describes in detail the mechanism and enzymes of NER in prokaryotes (pg. 46, 2nd full para. to pg. 52). The NER UvrABC DNA damage-specific endonuclease of *E. coli* is described in extensive detail in Friedberg (pg. 192-209), which discloses that the enzyme-catalyzed incision of damaged DNA during nucleotide excision repair in *E. coli* absolutely requires the UvrA, UvrB, and UvrC proteins (pg. 194, 1st full para). Thus, one skilled in the art, having read the present application, would have understood fully what was meant by a nucleotide excision-repair enzyme as recited in amended claim 78.

Therefore, the rejection of claim 78 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is improper and should be withdrawn.

The rejection of claims 79-80 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of the terms "*uvr* gene family" and "UvrB" enzyme is respectfully traversed.

With regard to the phrase "a *uvr* gene," the present application teaches that the DNA repair enzymes of the present invention include nucleotidase excision-repair (NER) enzymes, for example, those enzymes that are products of the *uvr* gene family, including the UvrB protein (pg. 15, lines 12-20). Moreover, it was known at the time the present invention was made that NER in bacteria is mediated by the gene products of the *uvrA*, *uvrB*, and *uvrC*

genes, as demonstrated by Theis, as discussed above; Orren et al., "Post-Incision Steps of Nucleotide Excision Repair in *Escherichia coli*: Disassembly of the UvrBC-DNA Complex by Helicase II and DNA Polymerase I," *J Biol Chem* 267(2):780-788 (1992) at Abstract and pg. 780, left col., 1st full para. ("Orren") (attached hereto as Exhibit 17) and Friedberg, which discloses that the *uvrA*, *uvrB*, *uvrC*, and *uvrD* genes are known to be involved in damage-specific base incision repair of DNA (pg. 192, 2nd full para.), and goes on to describe with specificity the structure and function of *uvrA* (pg. 194-197), *uvrB* (pg. 197-204), *uvrC* (204-206), and *uvrD* (pg. 210-213) gene products. Thus, the meaning of "a uvr gene" would have been fully understood by one of skill in the art.

With regard to the indefiniteness rejection of the term "UvrB enzyme" in claim 80, the structure of the bacterial UvrB enzyme was well characterized at the time the present invention was made as evidenced by Theis (pg. 279, rt. col., 3rd full para. to pg. 288, end of 1st full para.); Friedberg (pg. 197, last full para. to pg. 200, end of 1st para., including Figures 5-7); and Skorvaga et al., "The ß-Hairpin Motif of UvrB is Essential for DNA Binding, Damage Processing, and UvrC-Mediated Incisions," *J Biol Chem* 277(2):1553-1559 (2002) ("Skorvaga") (attached hereto as Exhibit 18), (pg. 1553, rt. col., 1st full para., to top of pg. 1554). Furthermore, the function of UvrB in the NER mechanism was well known, as evidenced by Sancar (pg. 50, 2nd full para. to pg. 52, line 3, and Figure 1, pg. 49, with legend to Figure at pg. 48); Theis (pg. 294, rt. col., last para. to pg. 298, line 3); Friedberg (p. 200, 1st full para. to pg. 204, end of 1st line); Skorvaga (pg. 1554, rt. col., last full para., to pg. 1559, left col., last para.), and Orren (whole document, generally).

Furthermore, the UvrB enzyme that is a product of the *uvrB* gene was identified in pathogens other than *M. tuberculosis* prior to the making of the present invention. For example, Theis, Sancar, Friedberg, Skorvaga, and Orren disclose a UrvB protein from *E. coli*. In addition, Friedberg teaches that *M. luteus* genes homologous to *uvrA* and *uvrB* of *E. coli* were cloned (pg. 223, 4th full para.). Friedberg also discloses that, based on nucleotide excision mechanism exhibited in several other prokaryotes, including *Salmonella typhimurium, Pseudomonas fluorescens, Streptococcus pneumoniae, Bacillus subtilis*, and *Mycoplasma genitalium*, it is reasonable to assume the nucleotide excision repair mechanism highly similar to that of *E. coli* is conserved in prokaryotes (pg. 225, 1st full para.). Thus, one skilled in the art would have understood what was meant by "a UvrB enzyme" and would have expected that such an enzyme can be found, not only in *M. tuberculosis*, but in other pathogens as well.

Accordingly, the rejection of claims 79-80 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of the terms "*uvr* gene family" and "UvrB" enzyme is improper and should be withdrawn.

The rejection of claims 1-6, 12-20, 63-68, and 74-87 under 35 U.S.C. § 112 (1st para.) for failure to comply with the written description requirement is respectfully traversed.

It the position of the USPTO that the instant claims lack written description for proteasomal and/or enzyme inhibitors used to inhibit proteasomal activity. Applicants disagree.

In particular, applicants submit that one of ordinary skill in the art, having read the present application, would have understood that applicants were in full possession of the claimed invention.

Firstly, the present application teaches in great detail that resistance to the antimicrobial effect of nitrosative/oxidative stress damage from host cells is a key factor in persistent pathogenic infection, for example, infection of human hosts by *Mycobacterium tuberculosis* (Mtb) (pg. 2, line 19 to pg. 3, line 15; pg. 4, lines 16-21). The present application also teaches with specificity the role of proteasomes, i.e, to degrade short-lived regulatory proteins tagged by ubiquitin or related polypeptides, including the selective removal of mutant, damaged, and misfolded proteins (pg. 25, lines 6-10).

Furthermore, the present application teaches with great specificity that the protease inhibitors MLN-273 and epoxomicin blocked the ability of Mtb to overcome nitrite-mediated injury, a type of antibacterial host defense (Example 11 at pg. 33, line 12 to pg. 34, line 8 and Figures 11A-D; Figures 12A-B; Figures 13A-B; and Figures 14A-D). In addition, it was known in the art at the time the invention was made that MLN-273 (also known as PS-341) and epoxomicin are "extremely selective" proteasome inhibitors which may interfere directly with the proteolytic activity of the 20S core of the 26S eukaryotic proteasome (Adams, J., "Proteasome Inhibitors as New Anticancer Drugs," *Current Opinions in Oncology* 14:628-634 (2002) at pg. 629, left col., 1st full para. and rt. col., para. 4-5) (attached hereto as Exhibit 19) Thus, the present application teaches that inhibitors known to be effective inhibitors of eukaryotic proteasomal activity can also be used as inhibitors of prokaryotic proteasomal core activity. Moreover, at the time the present invention was made, additional compounds were known that were capable of inhibiting 26S proteasomal catalytic activity in the same order of magnitude as epoxomicin (Elofsson et al., "Toward Subunit-

Specific Proteasome Inhibitors: Synthesis and Evaluation of Peptide α'β'-Epoxyketones," *Chemistry and Biology* 6:811-822 (1999) at 815, left col., 3rd full sentence ("Elofsson") (attached hereto as Exhibit 20), and a compound was identified that was more powerful and more selective than MLN-273 (pg. 816, left col., 1st full para., and Table 4). Also known in the art was the chemistry and mechanism of a highly potent class of proteasome inhibitors, known as the peptide boronates, to which MLN-273 belongs (Kisselev et al., "Proteasome Inhibitors: from Research Tools to Drug Candidates," *Chem. Biol.* 8(8):739-758 (2001) at Table 3, Figures 5 (listed as PS-341)(attached hereto as Exhibit 21). As noted in "Methodology for Determining Adequacy of Written Description," *Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112s ¶1, "Written Description Requirement* 66 Fed. Reg. 1099, 1106 (2001); what is conventional or well known to one in the art need not be disclosed in detail.

Thus, the scope of the claims is entirely appropriate. It is clear from the present application that applicants have invented a method for treating pathogen infection that involves inhibiting proteasomal activity in a pathogen to make the pathogen susceptible to antibacterial host defenses. Since one skilled in the art would have understood that applicants were in possession of the claimed invention, the rejection of claims 1-6, 12-20, 63-68, and 74-87 under 35 U.S.C. § 112 (1st para.) for failure to comply with the written description requirement is improper and should be withdrawn.

The rejection of claims 1-6, 12-20, 63-68, and 74-87 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

It is the position of the USPTO that the specification is not enabling for the method of inhibiting proteasomal activity as claimed, because there is insufficient guidance for inhibitors of prokaryotic proteasomal activity. Applicants have summarized the disclosure of the present application with regard to inhibiting proteasomal activity in a prokaryotic pathogen to make the pathogen more susceptible to antibacterial host defenses *supra*. From that information, one of ordinary skill in the art would clearly have been able to make and use the present invention.

Therefore, the rejection of claims 1-6, 12-20, 63-68, and 74-87 under 35 U.S.C. § 112 (1st para.) for lack of enablement is improper and should be withdrawn.

In view of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: January 30, 2006

Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1304
Facsimile: (585) 263-1600

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